PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/036979	06.11.2004	06.11.2003

International Patent Classification (IPC) or both national classification and IPC
C07K7/06, C07K14/81, C07K19/00, A61K38/08, A61K38/16, C12N15/11

Applicant
GENENCOR INTERNATIONAL, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/036979

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-18(partially),19(complete);10-17 as to IA

because:

☒ the said international application, or the said claims Nos. 10-17 as to IA relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-18(partially),19(complete)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/036979

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. Invention 1:claims 1-18(partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-9,18
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1)Present claims 10-13 relate to the use in a method of a composition defined by reference to a desirable characteristic or property, namely that it comprises a peptide contained within a scaffold and that binds to a TGF-beta.
The claims cover the use of all compositions comprising peptides having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such peptides. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the peptide by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the peptides defined by SEQ ID Nos 2,4,6,8,10,12,14,16 and 18-34 (see however the next paragraph).

2)Due to lack of unity (see Box IV) only invention 1 as indicated in the ISR has been searched and consequently has been examined.

3)Claims 10-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

1)Reading the claims in the light of the description the problem to be solved could initially be considered to be the provision of peptides that bind to transforming growth factor (TGF), particularly TGF-ß, which can be used per se or in a defined protease resistant

scaffold for modulating hair growth.
2)This problem has been solved by a plurality of solutions as defined in respectively the independent claims 1, 18 and 19.
3)This plurality of solutions might, a priori, be considered as satisfying the requirements of unity in which the activity to bind to TGF-ß of the used compounds provides the special technical feature linking these different solutions.
4)However at the first priority date of the application use of compounds which bind to TGF-ß in order to reverse the hair growth inhibiting activity of TGF-ß was already known as can be illustrated by D1 (see abstract: use of antibody to TGF-ß to reverse the inhibiting activity).
5)In the light of this prior art, the ISA considers that a common technical link based on the activity to bind to TGF-ß, which could be the unifying concept, is no longer present.
6)The objective problem could therefore be considered to be the provision of alternative compounds that bind to TGF-ß for modulating hair growth.
7)Therefore unified solutions should relate to groups of compounds either a) sharing a common structural element which may be regarded as the special technical feature providing unity; this special technical feature should be an essential structural part common to all of the embodiments of the claimed invention (and responsible for the inventive effect), and which is absent from any solution to the same problem disclosed in the prior art, or
b)belong to a recognized group of compounds.
8)Regarding all of the proposed solutions as a whole, as defined in independent claims 1,18 and 19, it is considered that:
a)no common novel invariant structural features can be detected which could be considered as special technical feature providing unity to the application, and
b)there is no teaching in the application as a whole predicting that substituting one alternative by any of the others will lead to the same result, which would render said alternatives to belong to a recognized group of compounds.
10)As no other technical features can be distinguished which, in the light of the prior art, could be considered as special technical features on which a unifying concept could be based, there is lack of unity between the plurality of claimed inventions defined in the claims of the present application (see Rule 13.1 PCT). A subdivision in 23 inventions has been made as indicated in the ISR.
11)Due to the fact that every one of the subjects distinguished requires a separate search

for the structural concept and the covered compounds in databases and partially in the classified documentation, the ISA considers that the PCT Guidelines 10.64 and 10.65 regarding a complete search with negligible additional work, is certainly not applicable.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:
D1: J.Invest.Dermatol., 118:993-997, 2002

I.Novelty

D1 discloses the use of an antibody to reverse the inhibiting activity of TGF-ß to hair growth. Present claims 1 (and 18) and 3 relate respectively to a composition comprising a peptide consisting of the sequence CVTTDWIEC and a construct wherein said peptide is incorporated in a scaffold of a defined protease inhibitor. Hence the present claims 1-18 are considered to be novel under Art.33(2) PCT.

II.Inventive step

1)The closest prior art is considered to be D1, disclosing the use of an antibody to reverse the inhibiting activity of TGF-ß to hair growth.
2)The subject-matter of claims 1 and 18 essentially differs from said prior art therein that the composition comprises a short peptide that binds to TGF-ß.
3)The problem to be solved may therefore be considered to be the provision of an alternative compound binding to TGF-ß to be used in modulating hair growth..
4)There was no indication or suggestion in the prior art as to the present compound and its ability to bind to TGF-ß. Consequently inventive step can be acknowledged if it actually solves the problem posed, that is: reversing the inhibiting activity of TGF-ß to hair growth. However at present the experimental data merely demonstrate that the present compound binds to TGF-ß. Any data showing that said binding also prevents the binding of TGF-ß to its receptor and consequently reverses its inhibitory activity to hair growth is absent. The

data in theTable on page 48 are very incomplete and rather indicate that said compound lacks said activity.
Consequently in view of the available experimental data it is considered to be unlikely that the present compound solves the problem posed and hence the claims 1 and 18 are considered to lack inventive step under Art.33(3) PCT.

For the same reasons, mutatis mutandis, the dependent claims 2-17, having considered any feature thereof in combination with the features of any claim to which they refer, do not meet the requirements of the PCT in respect of inventive step.

III. Industrial applicability

For the assessment of the present claims 10-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

In claim 16 the expression "...under conditions such that the activity .... is decreased" is not clear contravening Art.6 PCT.